AP/1615
IFW

IN THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant: Douglas Shepard

Serial No.: 10/057,596

Filed: January 24, 2002

Title: MEDICAL ARTICLES HAVING ENZYMATIC SURFACES FOR LOCALIZED THERAPY

Art Unit: 1615

Examiner: Gollamudi Kishore, Ph.D.

Confirmation No.: 2926

Docket No.: 01-531/4010-23

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REPLY BRIEF UNDER 37 C.F.R. §41.41

Sir:

This is a reply pursuant to 37 C.F.R. §1.193(b) in response to the Examiner's Answer mailed on December 27, 2006, in the appeal from the Examiner's decision dated April 15, 2005, finally rejecting Claims 1, 11-24, and 27 in the above-referenced patent application. A response is due within two months of the Examiner's Answer mailed December 27, 2006 and thus is being timely filed.

I. REAL PARTY IN INTEREST

Boston Scientific Scimed, Inc. is the assignee of the present invention and the real party in interest.

II. RELATED APPEALS AND INTERFERENCES

The statement contained in the Appeal Brief indicating that there are no related appeals or interferences for this application or any related co-pending applications is incorporated herein by this reference.

III. STATUS OF CLAIMS

The statement contained in the Appeal Brief indicating the status of the claims is incorporated herein by this reference. In the Examiner Answer, the Examiner confirmed that the statement of status of claims is correct.

IV. STATUS OF AMENDMENTS

The claims have not been amended after the final rejection. As indicated in the Appeal Brief and confirmed in the Examiner's Answer, the Appellant did not amend any of the claims subsequent to the final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The summary of the invention contained in the Appeal Brief is incorporated herein by this reference and was confirmed in the Examiner's Answer as correct.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

In the Examiner's Answer, the Examiner stated that he has withdrawn the reference Forster et al. (Am. J. Surg., Vol. 156, No. 2, August 1988) from the rejections. Thus, the following grounds of rejection remain and are presented for review:

Claims 1, 13-16 and 19-24 stand finally rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,855,234 (Hendrickson) or U.S. Patent No. 5,788,678 (Van Antwerp) by themselves or in combination further in view of U.S. Patent No. 5,741,331 (Pinchuk).

Claims 17 and 18 stand finally rejected under 35 U.S.C. §103(a) as being unpatentable over Hendrickson or Van Antwerp alone or taken together with Pinchuk and further in view of the acknowledged state of the art.

Claims 1, 11-16, 19-24 and 27 stand finally rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,569,688 (Sivan) taken together with Pinchuk.

Claims 17 and 18 stand finally rejected under 35 U.S.C. §103(a) as being unpatentable over Sivan and Pinchuk taken together with the acknowledged state of the art.

VII. CLAIMS APPENDIX

A copy of the claims involved in this appeal that were contained in the Appeal Brief and confirmed in the Examiner's Answer as correct is attached to this Reply Brief as ***XIV. Claims Appendix.***

VIII. EVIDENCE RELIED UPON

The following legal authorities are relied upon by Appellant in the following argument of this Reply Brief in the order in which they are cited:

Akso N.V. v. U.S. International Trade Commission, 808 F.2d 1241, 1480-81, 1 U.S.P.Q.2d, 1241, 1246 (Fed. Cir. 1986), *cert. denied,* 482 U.S. 909 (1987); and

Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 874, 228 U.S.P.Q. 90-99 (Fed. Cir. 1985);

In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992);

Ecolochem, Inc. v. Southern Calif. Edison Co., 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1076 (Fed. Cir. 2000); and

MPEP § 2143.02

IX. ARGUMENT

In the *Examiner's Answer*, page 4, line 16-20, the Examiner states that

> Appellant argues that the examiner has failed to recognize the structural significance of appellant's claimed polymeric matrix article wherein an enzyme is an integral part of the polymeric matrix and not merely coated or immobilized onto a solid surface. The examiner disagrees since *each of the primary references teaches an article and a*

> *matrix in which the enzyme is immobilized.* For example, Hendrickson clearly teaches devices (articles) and the enzyme is immobilized with the use of a polymer (emphasis added).

In reply, Appellant disagrees with the Examiner's assertion that each of the primary references teaches an article and a matrix in which the enzyme is immobilized.

Regarding Hendrickson, Appellant states that Hendrickson discloses fibrous supports made of woven and nonwoven webs of polymer (Hendrickson, col. 2, lines 34-45). Hendrickson discusses the difficulties and challenges of immobilizing proteins such as enzymes in these polymer webs. Presented with this challenge, Hendrickson teaches the necessity of subjecting the polymer fibrous supports to a surface modification treatment such as "plasma treatment" then providing "a layer of a protein immobilizer compound" to provide binding sites for binding the enzyme to the protein immobilizer compound (Hendrickson, col. 2, lines 34-39; col. 5, lines 4-26).

> Fibrous supports, such as woven and particularly nonwoven webs, because of their ease of handling and high surface area, provide desirable constructions upon which proteins such as enzymes can be immobilized. It has been found, however, that some of the typical polymers used to make woven and nonwoven webs, *such as polyalkylenes, do not irreversibly absorb or bind the protein immobilizers known to the art.* Immobilized proteins such as enzymes can retain a substantial portion of their biological activity even though bound to a support. *Surprisingly, it has been found that certain polymers, including polyalkylenes, commonly used to make nonwoven webs can be used as supports for protein immobilization* ***if their surface is first subjected to a modification treatment capable of providing binding sites for a protein immobilizer compound.*** It has not previously been known to treat woven and nonwoven webs for the purpose of providing binding sites for chemical additives. (Emphasis added).

Looking to Example 1 of Hendrickson, for example, Hendrickson discloses "data [that] show that a plasma treatment can produce binding sites for protein immobilizers on BMF [polypropylene blown microfiber] pads, and the pads are useful in the construction of the present invention." (col. 10, lines 28-32). Thus, the enzyme is not disposed within a block copolymer matrix as provided in

claim 1. Rather, the enzymes of Hendrickson ***are bound to binding sites on an intermediate layer of a protein immobilizing compound***. Given these teachings of Hendrickson, Appellant respectfully states that Hendrickson teaches away from the present invention wherein an enzyme is directly disposed within the block copolymer matrix. Rather, Hendrickson teaches that the enzyme must be bound to an intermediate protein immobilizing layer and not to the polymer fibrous support itself. Thus, Appellant respectfully asserts that the Examiner is erroneous in his finding that Hendrickson teaches the claimed article having an enzyme disposed within a block copolymer matrix.

In the *Examiner's Answer*, page 3, lines 12-14, the Examiner states that

> Hendrickson discloses devices wherein enzymes catalase and papain are immobilized on the surfaces. This *layer is further coated with a polymer* (note columns 4, 7-9, and claims 1 and 9)(emphasis added).

In response, Appellant states that the polymer coating to which the Examiner refers teaches away from the claimed block copolymer matrix. As claimed, the polymer matrix of Appellant's invention has "an enzyme disposed within said matrix...such that medical article is provided with an enzymatically active surface" and the "matrix allows diffusion of substrates into and diffusion of products out of the matrix." In contrast, Hendrickson teaches a polymer barrier coating (separate and apart from the fibrous polymer webs) that can be applied to the composite article to "prevent[] the enzyme from neutralizing the hydrogen peroxide and slowly dissolves in the hydrogen peroxide solution." Thus, rather than providing the article with an enzymatically active surface, the polymer barrier coating of Hendrickson causes the "activity of the enzyme in neutralizing hydrogen peroxide...[to] be *attentuated* [sic] by use of controlled release technology." (Hendrickson, col. 4, lines 3-16)(emphasis added).

Given such disclosure, the coating of Hendrickson appears to ***impair***, rather than ***facilitate*** enzymatic activity and thus, Appellant states that one of

ordinary skill in the art would not substitute the polymer matrix of the present invention which has enzyme disposed within the matrix of the Appellant's invention with any of the coatings or fibrous polymer webs of Hendrickson to arrive at the enzymatically active medical articles of the present invention.

Regarding Van Antwerp, the Examiner states in the *Examiner's Answer*, page 3, lines 15-17, that

> Antwerp discloses indwelling catheters coated with fibrinolytic enzymes. The enzymes in turn are encapsulated and bonded to the surface of the catheter (columns 2-6 and claims).

In response, Appellant asserts that Van Antwerp provides no disclosure of incorporation of the enzyme within a polymer matrix or any block copolymers of any type. Rather, Van Antwerp teaches a surface coating with enzyme particles that are "mechanically trapped or retained against the surface of the catheter 10 by an encapsulating film 18 selected for secure film adhesion to the polymeric catheter material." (Van Antwerp, col. 4, lines 26-34). Van Antwerp does not teach a block copolymer matrix having enzymes disposed within the matrix. Rather, it teaches a "surface coating comprising time release capsules having an enzyme contained within an encapsulating shell." (col. 6, lines 44-50). Appellant respectfully states that one of ordinary skill in the art would not find it obvious to substitute the claimed block copolymer matrix having enzyme disposed within the matrix with the time release capsules of Van Antwerp and combine it with the materials of Pinchuk to arrive at the present invention.

Regarding Sivan, in the *Examiner's Answer*, page 7, lines 7-13, the Examiner states that

> Sivan discloses an intravascular apparatus wherein nitric oxide synthase is covalently attached to the carrier. The enzyme either chemically attached [sic] to the stent or *alternatively entrapped within a polymeric hydrogel that covers the stent. The polymeric material includes polymers and copolymers such as polyethylene, polypropylene, polyacrylic acid and others* (col. 3, line 41 through col. 5, lines 9 and

> claims 1 and 4). What is lacking in Sivan is the use of claimed block copolymer comprising polybutylene and acrylates or vinyl aromatics.

In response, Appellant states that the Examiner has mischaracterized the teaching of Sivan. The Examiner states that Sivan discloses that the polymeric hydrogel can be made of "polyethylene, polypropylene, polyacrylic acid and others," implying that Sivan provides support for an enzyme entrapped in a variety of polymeric hydrogels. This is incorrect. What the Examiner has stated as polymeric hydrogel materials are in fact, "stent" materials (see, col. 3, lines 60-67) and ***not*** a recitation of polymeric hydrogel materials. As stated in the Abstract and the Summary of the Invention of Sivan, Sivan is focused on direct immobilization of the enzyme onto the surface of the article. As an alternative to direct bonding, Sivan teaches that "the enzymes may be entrapped within a polymeric hydrogel network" (col. 5, lines 4-5). However, Sivan is ***very specific*** about the materials and procedures for such polymeric hydrogel network and provides a single, specific polymerization reaction as follows:

> Alternatively, the enzymes may be entrapped within a polymeric hydrogel network covering the stent by means of the following procedure: (i) treatment of the stent with 3-acryloxypropyl trimethoxysilane; and (ii) photopolymerization of a mixture of the enzyme and alpha, omega-diacryloyl polyethylene glycol. (col 5, lines 4-9).

Appellant states that the above disclosure does not relate to an enzyme within a block copolymer matrix, but rather, to an ***interpolymer*** of an acryloxysilane, diacrolyl polyethylene glycol and the enzyme, so that the resulting polymer is formed from the enzyme itself. There is nothing in Sivan to indicate that such an interpolymer can be created using the polymer materials of Pinchuk to result in the medical articles of the present invention. In fact, there are no examples or teachings in Sivan to indicate that any polymeric hydrogel other than the specific reaction described can be achieved. There are no examples or claims in Sivan directed to such an enzyme entrapped within such a polymeric hydrogel network.

The Examiner further turns to Pinchuk for its purported teaching of relevant polymers for various types of implantable articles. *See* column 1, lines 33-40. Pinchuk

discloses block and star copolymers for various types of implantable medical devices. However, Pinchuk fails to remedy the deficiencies in Henderson, Van Antwerp or Sivan that are cited above. There appears to be no teaching in Pinchuk of an enzymatically active polymeric matrix, nor does there appear to be any teaching regarding diffusion of enzymatic substrates into, and diffusion of enzymatic products out of, a matrix. In addition, there can be found within the combination of references no suggestion or motivation to use the polymers of Pinchuk in the devices of the other references. Thus, to make such a combination and make a conclusion of obviousness could only be based on the use of *undue* hindsight, which has long been held to be impermissible. See, for example, *Akso N.V. v. U.S. International Trade Commission*, 808 F.2d 1241, 1480-81, 1 U.S.P.Q.2d, 1241, 1246 (Fed. Cir. 1986), *cert. denied,* 482 U.S. 909 (1987); *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 874, 228 U.S.P.Q. 90-99 (Fed. Cir. 1985).

Appellant asserts that the Examiner has not provided sufficient evidence to support a *prima facie* case of obviousness. The Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Fritch*, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992). An adequate showing of motivation to combine requires "evidence that 'a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.'" *Ecolochem, Inc. v. Southern Calif. Edison Co.*, 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1076 (Fed. Cir. 2000).

Appellant asserts that the evidence cited by the Examiner would not have provided one of ordinary skill in the art with sufficient motivation to substitute the specific block copolymer matrices of the present invention having an enzyme disposed within said matrix for the fibrous polymer supports with a protein immobilizing layer of Hendrickson, the time release capsules of Van Antwerp, or the silane-based polymeric hydrogel network of Sivan to arrive at the present invention. In particular, the Examiner

has not indicated, or shown where the references disclose that the disclosed polymer matrix with enzyme disposed within can be incorporated into or adapted to the fibrous article of Hendrickson, the catheter of Van Antwerp, or the intravascular apparatus of Sivan when combined with the materials of Pinchuk. The Examiner has also chosen to ignore teachings in Hendrickson that would teach away from combining the cited references to arrive at the present invention.

In view of the above, Appellant asserts that the Examiner has not provided sufficient evidence that one of ordinary skill in the art confronted with the same problems as the inventor, i.e., providing enzymatically active medical articles for localized supply of drugs and localized removal of undesirable chemical entities from a site, and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed, to support a *prima facie* case of obviousness. Appellant asserts that the prior art presented by the Examiner fails to provide such motivation.

The Examiner has also failed to explain why there would have been a reasonable expectation of success of producing the claimed medical articles from these teachings. *See* MPEP § 2143.02 and the cases cited therein. The Examiner also failed to show how the cited references teach or suggest the claimed functional limitations regarding the "diffusion" action of the enzymatic substrates.

Thus, the Henderson, Van Antwerp and Sivan references, either singly or in combination with Pinchuk, fail to establish a *prima facie* case of obviousness. Accordingly, reconsideration and withdrawal of the rejections as being unpatentable over Hendrickson, Antwerp or Sivan, each taken alone or in view of Pinchuk, is therefore requested.

For at least these reasons, it is respectfully submitted that claim 1 is patentable over the cited references. Claims 11-24 and 27 depend upon claim 1 and are therefore patentable for at least the same reasons as is claim 1.

X. CONCLUSION

The references relied on by the examiner do not support a *prima facie* case of obviousness. Thus, it is respectfully submitted that reversal of the rejections of record is in order.

XI. FEES

Appellant's undersigned representative hereby authorizes the Commissioner to charge any fees due and owing with respect to the filing of this paper to deposit account No. 50-1047.

Respectfully submitted,

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(Printed Name of Person Mailing Correspondence)

 (Signature)

XII. EVIDENCE APPENDIX

None.

XIII. RELATED PROCEEDINGS APPENDIX

None.

XIV. CLAIMS APPENDIX

1. (Previously presented) An enzymatically active medical article comprising:
a medical article having a matrix disposed on said article, wherein the matrix comprises a block copolymer comprising a polyolefinic block comprising polybutylene and a thermoplastic block comprising polymers of acrylates, methacrylates or vinyl aromatics, an enzyme disposed within said matrix and at or near a surface of said medical article, such that said medical article is provided with an enzymatically active surface, wherein said matrix allows diffusion of substrates into and diffusion of products out of the matrix, wherein said enzyme is elected from the group consisting of protease enzymes, glycosidase enzymes, enzymes that degrade oxalate, and enzymes that generate NO from arginine.

2. (Withdrawn) The enzymatically active medical article of claim 1, wherein said enzyme is a protease enzyme.

3. (Withdrawn) The enzymatically active medical article of claim 1, wherein said enzyme is an enzyme that degrades cholesterol esters.

4. (Withdrawn) The enzymatically active medical article of claim 3, wherein said enzyme is selected from cholesterol esterase and cholesterol oxidase.

5. (Withdrawn) The enzymatically active medical article of claim 1, wherein said enzyme is an enzyme that converts hydrocortisone to cortisone.

6. (Withdrawn) The enzymatically active medical article of claim 5, wherein said enzyme is a hydrocortisone esterase enzyme.

7. (Withdrawn) The enzymatically active medical article of claim 1, wherein said enzyme is a glycosidase enzyme.

8. (Withdrawn) The enzymatically active medical article of claim 7, wherein said enzyme is an α-galactosidase enzyme.

9. (Withdrawn) The enzymatically active medical article of claim 7, wherein said enzyme is a β-galactosidase enzyme.

10. (Withdrawn) The enzymatically active medical article of claim 7, wherein said enzyme is a β-glucosidase enzyme

11. (Original) The enzymatically active medical article of claim 1, wherein said enzyme is an enzyme that generates NO from arginine.

12. (Original) The enzymatically active medical article of claim 11, wherein said enzyme is nitric oxide synthetase.

13. (Original) The enzymatically active medical article of claim 11, wherein said enzyme is provided within a biocompatible, biostable matrix coating disposed on said medical article.

14. (Original) The enzymatically active medical article of claim 11, wherein said enzyme is attached to a surface of said medical article.

15. (Original) The enzymatically active medical article of claim 14, wherein said enzyme is covalently attached to a surface of said medical article.

16. (Original) The enzymatically active medical article of claim 14, wherein said enzyme is attached to a surface of said medical article by ion exchange forces.

17. (Original) The enzymatically active medical article of claim 14, wherein said enzyme is attached to a surface of said medical article by antibody-antigen interactions.

18. (Original) The enzymatically active medical article of claim 14, wherein said enzyme is attached to a surface of said medical article by nucleic-acid hybridization.

19. (Original) The enzymatically active medical article of claim 14, wherein said enzyme is attached to a surface coating on said medical device.

20. (Original) The enzymatically active medical article of claim 1, further comprising an enzyme-free coating layer provided over said enzyme, wherein said enzyme-free coating layer acts to hide said enzyme from immune surveillance.

21. (Original) The enzymatically active medical article of claim 1, wherein said medical article is a vascular medical device.

22. (Original) The enzymatically active medical article of claim 1, wherein said medical article is selected from a catheter, a guide wire, a balloon, a filter, a stent, a stent graft, a cerebral aneurysm filler, a vascular graft, a heart valve, a bandage and a bulking agent.

23. (Original) A therapeutic method comprising:

providing the enzymatically active medical article of claim 1; and

administering said medical article to a patient.

24. (Original) The therapeutic method of claim 23, wherein said medical article is a vascular medical device.

25. (Withdrawn) The therapeutic method of claim 23, wherein said enzyme is an enzyme that converts hydrocortisone to cortisone and wherein said medical article is administered to a site of inflammation.

26. (Withdrawn) The therapeutic method of claim 23, wherein said enzyme is an enzyme that converts hydrocortisone to cortisone and wherein said medical article is administered to a site of inflammation.

27. (Original) The therapeutic method of claim 23, wherein said enzyme is an enzyme that generates NO from arginine and wherein said medical article is administered to a site within the vasculature to prevent restenosis.

28. (Withdrawn) The therapeutic method of claim 23, wherein said enzyme is an enzyme that acts upon cholesterol esters and wherein said medical article is placed adjacent atherosclerotic plaque within the vasculature to degrade the cholesterol ester deposits found in said atherosclerotic plaque.

29. (Withdrawn) The therapeutic method of claim 23, wherein said enzyme is a glycosidase enzyme effective to degrade ceramide trihexoside in the treatment of Fabray's disease and wherein said medical article is a blood contacting device.

30. (Withdrawn) The therapeutic method of claim 23, wherein said enzyme is a glycosidase enzyme effective to degrade glycocerebroside in the treatment of Gaucher's disease and wherein said medical article is a blood contacting device.

31. (Withdrawn) The therapeutic method of claim 23, wherein said enzyme is a glycosidase enzyme effective to degrade ganglioside GM2 in the treatment of Tay-Sach's disease and wherein said medical article is implanted within the cranium.

32. (Withdrawn) The therapeutic method of claim 23, wherein said enzyme is oxalate oxidase and wherein said medical article is a urinary catheter.

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1. 16-page Reply Brief Under 37 CFR 41.41